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Strength, But Not Muscle Mass, Is Associated With Mortality in the Health, Aging and Body Composition Study Cohort

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Background. Although muscle strength and mass are highly correlated, the relationship between direct measures of low muscle mass (sarcopenia) and strength in association with mortality has not been examined.

Methods. Total mortality rates were examined in the Health, Aging and Body Composition (Health ABC) Study in 2292 participants (aged 70–79 years, 51.6% women, and 38.8% black). Knee extension strength was measured with isokinetic dynamometry, grip strength with isometric dynamometry. Thigh muscle area was measured by computed tomography (CT) scan, and leg and arm lean soft tissue mass were determined by dual energy x-ray absorptiometry (DXA). Both strength and muscle size were assessed as in gender-specific Cox proportional hazards models, with age, race, comorbidities, smoking status, level of physical activity, fat area by CT or fat mass by DXA, height, and markers of inflammation, including interleukin-6, C-reactive protein, and tumor necrosis factor-α considered as potential confounders.

Results. There were 286 deaths over an average of 4.9 (standard deviation = 0.9) years of follow-up. Both quadriceps and grip strength were strongly related to mortality. For quadriceps strength (per standard deviation of 38 Nm), the crude hazard ratio for men was 1.51 (95% confidence interval, 1.28–1.79) and 1.65 (95% confidence interval, 1.19–2.30) for women. Muscle size, determined by either CT area or DXA regional lean mass, was not strongly related to mortality. In the models of quadriceps strength and mortality, adjustment for muscle area or regional lean mass only slightly attenuated the associations. Further adjustment for other factors also had minimal effect on the association of quadriceps strength with mortality. Associations of grip strength with mortality were similar.

Conclusion. Low muscle mass did not explain the strong association of strength with mortality, demonstrating that muscle strength as a marker of muscle quality is more important than quantity in estimating mortality risk. Grip strength provided risk estimates similar to those of quadriceps strength.

OLDER adults with reduced muscle strength have higher mortality (1–6). Muscle strength is closely related to the absolute quantity of muscle mass, which is also reduced with aging (7–10). This decrease in muscle mass (sarcopenia) is thought to contribute to the development of functional limitations and disability in old age (11,12), and potentially might explain part of the association between strength and mortality. Previous studies (1–4) have used only weight, creatinine excretion, or derived anthropometric measures to estimate muscle mass. Thus the role of muscle mass in mediating the strength–mortality association has not been adequately determined.

Strength might also predict mortality because it is reduced with disease and deconditioning. For example, lower extremity arterial ischemia can cause lower muscle strength and function (13). Pain from osteoarthritis may prevent activity resulting in atrophy from disuse. Intervention studies show the potential for large improvements in strength with small increases in lean mass (14), illustrating the importance of activity and exercise. Markers of inflammation are also related to lower strength (15) and lean mass, as well as to a decline in strength (16). However, in the Women's Health and Aging Study, comorbidity and inflammatory markers did not explain the association of lower grip strength with mortality (3).

The Health, Aging and Body Composition (Health ABC) Study was designed to determine the role of body composition changes in the risk of poor health outcomes including death and functional limitation in older adults. In this report, we sought to determine whether low muscle mass, measured with computed tomography (CT) scanning and dual energy x-ray absorptiometry (DXA), would ex-

plain an association of strength with mortality with and without adjusting for hypothesized causes of sarcopenia, including physical activity, disease, and inflammatory markers. Finally, we were able to compare associations on the basis of isokinetic quadriceps strength versus isometric grip strength.

Methods

Population

The Health ABC Study cohort included 3075 men (48.4%) and women (51.6%) aged 70–79 years, of whom 41.6% are African American. Recruitment and eligibility have been described (7). Briefly, participants were sampled and recruited from Medicare listings in Pittsburgh, Pennsylvania, and Memphis, Tennessee. Eligibility criteria included: age 70–79 years, self-report of no difficulty walking one-quarter mile or climbing 10 steps, or with activities of daily living, no history of active treatment for cancer in the prior 3 years, and no plan to move out of the area. All participants gave informed consent, and the consent forms and protocol were approved by the institutional review boards at each field center. For the present analysis, only those persons with complete data for strength and body composition were included ($n = 2292$).

Outcome

Total mortality was assessed over 6 years with a mean follow-up of 4.9 (standard deviation [*SD*] 0.9) years. Surveillance was conducted by in-person examination or telephone interview every 6 months. Hospital records, death certificates, informant interviews, and autopsy data were reviewed by committee to adjudicate immediate and underlying causes of death. The number of individual causes of death was too low to have adequate power to assess risk for cause-specific mortality at this time.

Strength Assessments

Strength was measured using an isokinetic Kin-Com dynamometer (model 125 AP; Chattanooga, TN) for knee extension and an isometric dynamometer (Jaymar, Bolingbrook, IL) for grip strength. For knee extension, the right leg was used unless contraindicated by pain or history of joint replacement. Participants with uncontrolled hypertension, stroke, bilateral knee replacement, or severe bilateral knee pain were excluded from the test (7). Isometric grip strength was assessed for each hand. Participants with severe hand pain or recent surgery were excluded. The vast majority (96%) who had leg strength testing also had grip strength testing. For these analyses, we used the maximum of the force from two trials for the right upper extremity. The ratio of muscle size to strength (specific torque or force) (7) was calculated as a marker of the quality of the muscle and was also considered as a predictor of mortality (7,17).

Body Composition

Lean mass of the upper and lower extremities as well as the total body were assessed using DXA (Hologic QDR 4500, software version 8.21; Waltham, MA). Bone mineral content was subtracted from the total and regional lean mass to define total nonbone lean mass, which represents primarily skeletal muscle in the extremities (18). Fat mass was estimated for the whole body as well. Both the percent fat and total fat were examined in these analyses. With the participant in a hospital gown and no shoes, body weight and height were measured by calibrated balance beam scale and stadiometer, respectively. Body mass index (BMI) in kilograms per meter squared was also examined as a measure of body composition. Analyses of the lower extremities were repeated using cross-sectional muscle and fat areas of the mid-thigh assessed by CT scan (in Pittsburgh: 9800 Advantage, General Electric, Milwaukee, WI; in Memphis: Somatom Plus 4, Siemens, Erlangen, Germany, and PQ 2000S, Marconi Medical Systems, Cleveland, OH) (17). All images were network transferred (Transmission Controlled Protocol/Internet Protocol) and analyzed by a single observer using a Sun workstation (SPARC station II; Sun Microsystems, Mountain View, CA) and proprietary Interactive Data Language development software (RSI Systems, Boulder, CO).

Other Covariates

Age, race, level of physical activity, total number of chronic conditions, smoking status, and field site were all considered as possible confounders of the association between strength and mortality. Physical activity was assessed by self-report as total kilocalories/week spent walking and exercising (19,20). Smoking status was assessed by questionnaire, and participants were classified as current, past, or never smokers. Depression score, assessed with the Center for Epidemiologic Studies-Depression (CES-D) scale (21), was examined as a potential marker of motivation because voluntary assessment of strength was used. Using self-report with confirmation by treatment and medications, we assessed comorbidity as the total number of 11 chronic health conditions. These conditions included cancer, myocardial infarction, congestive heart failure, depression, diabetes, hypertension, knee osteoarthritis, osteoporosis, peripheral arterial disease, pulmonary disease, and stomach and/or duodenal ulcer. Inflammatory markers were assessed from stored fasting blood specimens. Interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) were measured in duplicate using enzyme-linked immunosorbent assay kits (R&D Systems, Minneapolis, MN). C-reactive protein serum levels were also measured in duplicate using enzyme-linked immunosorbent assay based on purified protein and polyclonal anti-C-reactive protein antibodies (Calbiochem, San Diego, CA) (22).

Analysis

Means and proportions were used to describe demographic and key clinical characteristics of the study population. Because there was minimal overlap in strength or body composition between men and women, all analyses were stratified by gender. Quadriceps and grip strength were examined as continuous variables. After assessing the proportionality assumption, we used the Cox proportional hazards model to assess the association between strength and mortality. Hazard ratios (HR) and 95% confidence

Table 1. Baseline Demographics, Anthropometrics, Strength, and Body Composition

Characteristics	Men $N = 1124$	Women $N = 1168$
Demographics		
Age, mean y (*SD*)	73.7 (2.9)	73.4 (2.8)
Race		
Black, %	34.8	42.6
White, %	65.2	57.4
Education		
< High school, %	26.4	21.6
High school, %	25.7	40.7
> High school, %	47.9	37.7
Anthropometrics		
Weight, kg (*SD*)	81.1 (12.7)	69.9 (13.9)
Height, cm (*SD*)	173.2 (6.4)	159.6 (6.2)
Body mass index, mean kg/m^2 (*SD*)	27.0 (3.8)	27.4 (5.2)
Strength		
Grip, mean kg (*SD*)	40.8 (8.5)	25.1 (5.8)
Quadriceps, mean Nm (*SD*)	132.1 (33.8)	81.3 (21.7)
CT body composition		
Muscle area—right leg, mean cm^2 (*SD*)	132.6 (22.2)	92.6 (17.1)
Subcutaneous fat area, mean cm^2 (*SD*)	46.9 (19.4)	105.6 (44.8)
Intermuscular fat area, mean cm^2 (*SD*)	9.7 (5.7)	10.3 (5.6)
DXA body composition		
Total fat mass, mean kg (*SD*)	23.1 (6.8)	28.2 (8.7)
Total lean mass, mean kg (*SD*)	55.3 (7.1)	39.8 (5.8)
Arm lean mass, mean kg (*SD*)	3.5 (0.6)	2.1 (0.4)
Leg lean mass, mean kg (*SD*)	8.8 (1.3)	6.4 (1.2)

Notes: *SD* = standard deviation; CT = computed tomography; DXA = dual energy x-ray absorptiometry.

intervals (CI) are reported. Results were expressed in the full cohort's *SD* for each strength measure to allow a comparison of the HR for quadriceps strength and for grip strength and between men and women. Separate models were used to first adjust for CT and then DXA body composition measures. Additional potential factors were considered using a forward stepwise procedure to adjust for age, race, height, inflammatory markers, smoking status, comorbidity count, level of physical activity, education, and depression score. Alternative models adjusting for individual health conditions were also examined, but did not change the main findings. Models were also examined with adjustment for BMI as an alternative to the more direct measures of lean and fat mass.

Results

Over the follow-up period, there were 286 deaths (180 in men and 106 in women), with mortality rates of 33.1 and 18.1 per 1000 person-years, respectively. At baseline (Table 1), the mean age was 73.7 years in men and 73.4 years in women. Strength and body composition of the cohort differed substantially in men and women, with women having substantially lower strength, lower lean mass and muscle area, and higher subcutaneous fat area and fat mass. Of note, the mean BMI was similar in men and women.

Both quadriceps and grip strength were strongly related to mortality. For quadriceps strength (per *SD* of 38 Nm), the crude HR was 1.51 (95% CI, 1.28–1.79) for men and 1.65 (95% CI, 1.19–2.30) for women (Table 2). In the models of quadriceps strength and mortality, adjustment for muscle area or regional lean mass only slightly attenuated the associations. There was also little evidence that the associations of quadriceps strength with mortality were due to demographic, behavioral, or health factors considered in the multivariate models. These factors only slightly attenuated the association of strength with mortality in both men and women. In the models adjusting for lean and fat mass using DXA, the association of quadriceps strength with mortality was reduced to a HR of 1.45 (95% CI, 1.21–1.74) in men and 1.47 (95% CI, 1.02–2.14) in women. When adjusting for lean and fat by CT scan, the attenuation of the HR for strength was slightly greater in the men. Regardless of whether DXA or CT was used, the other factors that were associated with mortality were similar. In

Table 2. Muscle Strength–Mortality Risk per Standard Deviation of Quadriceps or Grip Strength in Men and Women

Strength	No. of Deaths	Person-Years	Crude Rate per 1000 Person-Years	Unadjusted HR (95% CI)	HR (95% CI) Multivariate Adjustment Including DXA Body Composition*†	HR (95% CI) Multivariate Adjustment Including CT Body Composition†‡
Men						
Quadriceps strength (per 38.0 Nm)	180	5445	33.1	1.51 (1.28–1.79)	1.45 (1.21–1.74)	1.36 (1.12–1.65)
Grip strength (per 10.7 kg)				1.36 (1.13–1.64)	1.36 (1.10–1.60)	—
Women						
Quadriceps strength (per 38.0 Nm)	106	5855	18.1	1.65 (1.19–2.30)	1.47 (1.02–2.14)	1.56 (1.05–2.30)
Grip strength (per 10.7 kg)				1.84 (1.28–2.65)	1.67 (1.08–2.58)	—
Total						
Quadriceps strength (per 38.0 Nm)	286	11300	25.3	1.54 (1.32–1.79)§	1.45 (1.23–1.71)	1.39 (1.17–1.65)
Grip strength (per 10.7 kg)				1.45 (1.23–1.71)§	1.42 (1.17–1.71)	—

Notes: *DXA total fat, leg lean mass, or arm lean mass; — = no data available.

†All multivariate models were adjusted additionally for age and other factors in stepwise model including race, height, smoking status, physical activity level, number of chronic conditions, education, log interleukin-6, and Center for Epidemiologic Studies-Depression (CES-D) scale score.

‡CT subcutaneous and intermuscular fat.

§Adjusted for gender.

HR = hazard ratio; CI = 95% confidence interval; DXA = dual energy x-ray absorptiometry; CT = computed tomography.

Table 3. Muscle Size–Mortality Risk per Standard Deviation in Men and Women

Muscle Size Measure	HR (95% CI) Unadjusted	HR (95% CI) Multivariate Adjustment*
Men		
CT leg muscle area (per 28.1 cm^2)	1.32 (1.09–1.61)	1.26 (1.02–1.55)†
DXA leg lean (per 1.8 kg)	1.06 (0.87–1.30)	0.98 (0.75–1.28)‡
DXA arm lean (per 0.9 kg)	1.06 (0.84–1.33)	1.0 (0.76–1.33)‡ 2.0
Women		
CT leg muscle area (per 28.1 cm^2)	1.19 (0.86–1.64)	0.94 (0.66–1.35)†
DXA leg lean (per 1.8 kg)	1.16 (0.85–1.57)	0.96 (0.61–1.51)‡
DXA arm lean (per 0.9 kg)	1.12 (0.74–1.70)	1.0 (0.61–1.65)‡ 2.0
Total		
CT leg muscle area (per 28.1 cm^2)	1.29 (1.09–1.52)§	1.16 (0.97–1.39)†
DXA leg lean (per 1.8 kg)	1.09 (0.92–1.29)§	0.95 (0.76–1.20)‡
DXA arm lean (per 0.9 kg)	1.08 (0.89–1.32)§	0.99 (0.77–1.26)‡

Notes: *All multivariate models also adjusted additionally for age and other factors in stepwise model including race, height, smoking status, physical activity level, number of chronic conditions, education, log interleukin-6, and Center for Epidemiologic Studies-Depression (CES-D) scale score.

†CT subcutaneous and intermuscular fat.

‡DXA total fat, leg lean mass, or arm lean mass.

§Adjusted for gender.

HR = hazard ratio; CI = confidence interval; CT = computed tomography; DXA = dual-energy x-ray absorptiometry.

men, these included age, smoking status, number of chronic conditions, lower education, and higher IL-6; in women, they included age, smoking status, low physical activity, IL-6, and depression score. In men, height was associated with higher mortality in the multivariable model adjusted for CT measures but not in the model adjusting for DXA measures. CT measures of intermuscular fat and muscle attenuation were not related to mortality.

Unadjusted and adjusted associations of grip strength with mortality were similar to those for quadriceps strength. When considering an *SD* of grip strength (10.7 kg) to allow a comparison to an *SD* of quadriceps strength, the HRs were 1.36 (95% CI, 1.10–1.60) in men and 1.67 (95% CI, 1.08–2.58) in women. Factors that accounted for part of the association of grip strength with mortality and were significantly associated with mortality were essentially the same as for the models of leg strength and included age, smoking status, number of chronic conditions, lower education, and higher IL-6 in men and age, smoking status, low physical activity, and IL-6 in women. Of note, total fat mass tended to be protective; this was statistically significant in the men.

For both quadriceps and grip strength, the HRs for mortality appeared to be a little higher in women than in men. The CIs overlapped, and there was no evidence for a significant interaction between gender and strength on mortality. Adjustment for BMI yielded risk estimates similar to those shown for adjustment for lean and fat mass by DXA or for muscle and fat areas by CT scan.

Separate models for muscle size by DXA or CT scan were examined to further evaluate the lack of attenuation of strength by muscle size. In men, a lower leg muscle area on CT scan was related to a higher risk of mortality (adjusted HR = 1.26; 95% CI, 1.02–1.55) (Table 3). This was not the case in the women. Lean mass by DXA, either for the lower or the upper extremity, was not related to mortality in men or women. As would be expected from these results, the risks for specific torque or force (Table 4) were similar to those based on strength alone, showing adjusted relative risks 25%–40% higher per *SD* in both men and women.

Table 4. Specific Torque–Mortality Risk per Standard Deviation in Men and Women

Specific Torque Measure	HR (95% CI) Unadjusted	HR (95% CI) Multivariate Adjustment*
Men		
Quad strength/CT area (per 0.2 units)	1.32 (1.15–1.52)	1.26 (1.10–1.45)†
Quad strength/DXA leg lean (per 3.4 units)	1.49 (1.29–1.72)	1.39 (1.20–1.61)‡
Grip strength/DXA arm lean (per 2.5 units)	1.29 (1.10–1.52)	1.23 (1.05–1.45)‡
Women		
Quad strength/CT area (per 0.2 units)	1.27 (1.05–1.52)	1.24 (1.02–1.50)†
Quad strength/DXA leg lean (per 3.4 units)	1.29 (1.06–1.58)	1.24 (1.00–1.52)‡
Grip strength/DXA arm lean (per 2.5 units)	1.30 (1.09–1.55)	1.23 (1.02–1.49)‡
Total		
Quad strength/CT area (per 0.2 units)	1.30 (1.16–1.45)§	1.24 (1.11–1.40)†
Quad strength/DXA leg lean (per 3.4 units)	1.42 (1.26–1.59)§	1.34 (1.19–1.51)‡
Grip strength/DXA arm lean (per 2.5 units)	1.29 (1.15–1.46)§	1.23 (1.09–1.40)‡

Notes: *All multivariate models also adjusted for age and other factors in stepwise model including race, height, smoking status, physical activity level, number of chronic conditions, education, log interleukin-6, and Center for Epidemiologic Studies-Depression (CES-D) scale score.

†CT subcutaneous and intermuscular fat.

‡DXA total fat.

§Adjusted for gender.

HR = hazard ratio; CI = confidence interval; Quad = quadriceps; CT = computed tomography; DXA = dual energy x-ray absorptiometry.

The mortality rate was approximately 25%–30% higher in blacks than in whites. In men, there were 40.6 deaths per 1000 person-years in blacks (vs 29.1 in whites), and in women, 21.1 deaths in blacks (vs 15.9 in whites) per 1000 person-years. However, the association of low strength with mortality was similar in both groups, and tests for effect modification by race within gender groups were not significant.

To illustrate the patterns of association between strength and mortality, Kaplan–Meier survival curves were drawn for intervals of both quadriceps (Figures 1 and 2) and grip strength (Figures 3 and 4). The intervals of strength were chosen to approximate a gender-specific *SD* of strength to provide stable estimates of risk within gender. These figures show that the relationship of strength to mortality could be seen across the range of strength in this nondisabled cohort. There was no statistical evidence of any threshold in the association of either quadriceps strength or grip strength with mortality. Patterns of association were quite similar for both grip strength and quadriceps strength and in both men and women.

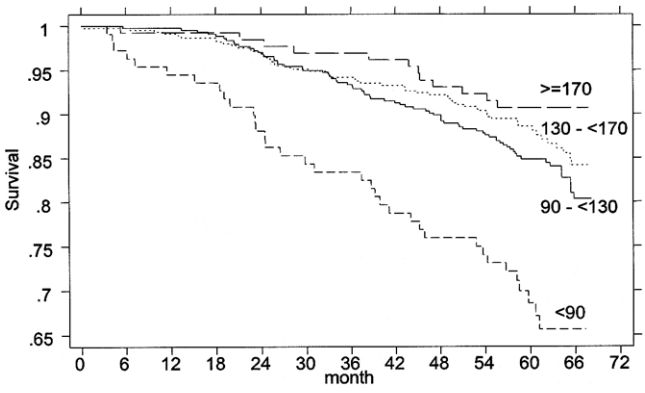

Figure 1. Men, leg strength, and mortality. Kaplan–Meier survival curves for leg strength groups (<90, 90–<130, 130–<170, ≥170 Nm). Intervals of 40 Nm of quadriceps strength were used to approximate men's standard deviation = 33.8 and to distribute the number of events.

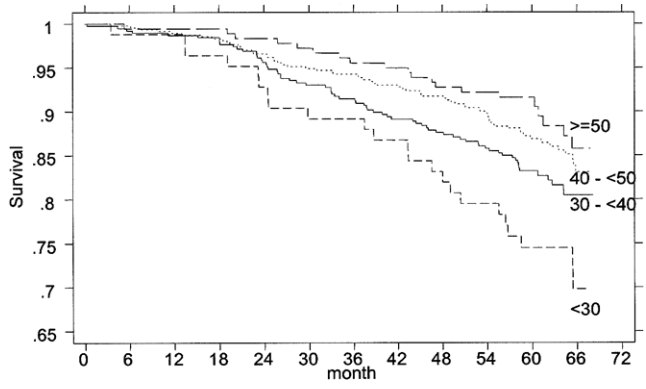

Figure 3. Men, grip strength, and mortality. Kaplan–Meier survival curves for grip strength groups (<30, 30–<40, 40–<50, ≥50 kg). Intervals of 10 kg of grip strength were used to approximate men's standard deviation = 8.5 and to distribute the number of events.

Discussion

This study confirms that measures of lower muscle strength, both quadriceps and grip, are strong and independent predictors of mortality in older adults. This association cannot be attributed to sarcopenia, as neither measure of muscle size attenuated the associations. In fact, lower muscle area by CT scan was the only measure of sarcopenia that was an independent predictor of mortality and this was only seen in the men. The strength–mortality association was not due to a higher level of inactivity or chronic illness in those participants with poor strength. The magnitude of association for both quadriceps and grip strength were similar, though perhaps slightly higher in women compared to men when using the same scale. These differences were not statistically significant, but may reflect that an interval strength on the same scale represents a larger relative increase in strength in the women than in the men. Although blacks had a higher mortality risk, the relative risk of mortality in relationship to strength was the same as in whites.

In epidemiological studies, grip strength has been assessed more widely than has leg strength and has been shown to be less strongly associated with age itself than has leg strength (7,8). Nevertheless, grip strength has been shown to be a robust predictor of mortality, even when measured in middle age (23). Grip strength is currently much easier to measure, thus has greater potential than would isokinetic dynamometry for incorporating into clinic practice. However, most studies report HRs based on cohort-specific lowest versus highest tertile or quartile of grip strength, so the exact magnitude of risk is difficult to evaluate across studies. Because there appears to be no threshold in this relationship, it may be helpful to report risk for standard intervals in future studies.

Previous studies have examined only men (1,2), or women (3); most have examined only grip strength, and none has adjusted for direct quantification of muscle area or lean mass as measures of sarcopenia. Nevertheless, all of these studies show consistent findings that suggest that muscle strength is a very important marker of mortality risk in old age. This association remains unexplained by sarcopenia, disease, activity level, and inflammatory markers in this study and in the Women's Health and Aging Study (3). This might be due to inadequate assessment of these factors, but more likely suggests that muscle strength may capture important aspects of the aging process that were not included in this analysis or in other studies. Potentially, strength-related hormonal factors such as

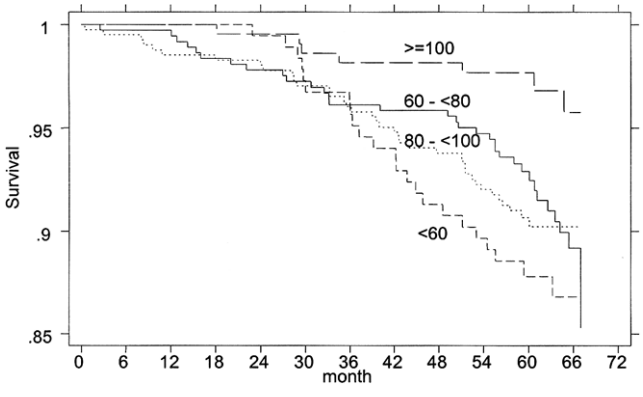

Figure 2. Women, leg strength, and mortality. Kaplan–Meier survival curves for leg strength groups (<60, 60–<80, 80–<100, ≥100 Nm). Intervals of 20 Nm of quadriceps strength were used to approximate women's standard deviation = 21.7 and to distribute the number of events.

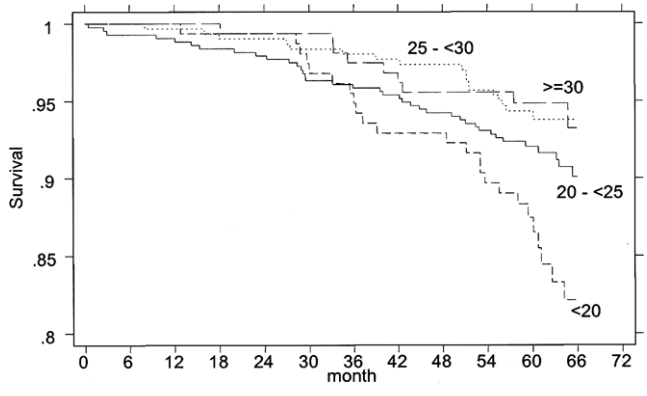

Figure 4. Women, grip strength, and mortality. Kaplan–Meier survival curves for grip strength groups (<20, 20–<25, 25–<30, ≥30 kg). Intervals of 5 kg of grip strength were used to approximate women's standard deviation = 5.8 and to distribute the number of events.

testosterone (24) and insulin-like growth factor-I (25,26), which decline with age and strength, might explain why strength appears to be such a powerful marker of risk. Assessment of these factors is in progress in the Health ABC Study.

The loss of motor neurons with aging results in an increase in size of remaining motor units, but with greater preservation of type 1 fibers, resulting in preservation of mass with relatively fewer type 2 fibers, thus lower strength (27). This neurogenic aspect of muscle aging is difficult to study without muscle biopsy, thus we are unable to determine whether this would explain the associations of strength but not mass with mortality.

The strengths of this study are the comparison of men and women and both upper and lower extremity strength, the use of state-of-the-art assessment of regional body composition, and the large number of minorities. DXA lean mass may overestimate lean mass in obese individuals because it includes intermuscular fat as lean mass. The similarity in the DXA and CT results suggests that this potential bias is not a major factor in these associations. To our knowledge, this is the first large epidemiologic study of African Americans. Strength has been shown previously to predict mortality in Caucasians (1), Hispanics, and Asians (2).

There are important characteristics of this study which limit the generalization of these findings. First, the Health ABC Study cohort was nondisabled at baseline. It is quite possible that measures of lean mass may be more important in individuals who are more disabled. Second, only 85% of this cohort was eligible for the isokinetic strength test. Analysis of these findings in the full cohort with grip strength alone was virtually identical, thus the exclusions do not appear to have biased the findings reported.

This study has important implications for clinical practice and future research. First, it shows that muscle function can be used to assess mortality risk without accounting for muscle size, and validates the use of grip strength against leg strength, which better isolates a specific muscle group but is harder to measure. Second, it demonstrates clearly that lower lean mass is not a predictor of mortality, thus cannot explain the strength–mortality association. These results do not explain why strength predicts mortality. More detailed assessment of lifelong activity; subclinical diseases; perhaps cognition, hormonal, or genetic factors; and of the primary changes in muscle with age are needed.

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